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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/398,399	09/17/99	DELENSTARR	G 10981620-1

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LEGAL DEPARTMENT 20BN
HEWLETT PACKARD COMPANY
P O BOX 10301
PALO ALTO CA 94303-0890

HM12/0524

EXAMINER	
SISSON, B	
ART UNIT	PAPER NUMBER
1655	17
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)
	09/398,399	DELENSTARR ET AL.
	Examiner Bradley L. Sisson	Art Unit 1655

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 09 April 2001.
- 2a) This action is **FINAL**. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 10-32 and 34-49 is/are pending in the application.
 - 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 10-32 and 34-49 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claims _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on _____ is/are objected to by the Examiner.
- 11) The proposed drawing correction filed on _____ is: a) approved b) disapproved.
- 12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

- 13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 - a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

- 15) Notice of References Cited (PTO-892)
- 16) Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 17) Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
- 18) Interview Summary (PTO-413) Paper No(s) _____
- 19) Notice of Informal Patent Application (PTO-152)
- 20) Other: _____

DETAILED ACTION

Continued Prosecution Application

1. The request filed on 9 April 2001 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/398,399 is acceptable and a CPA has been established. An action on the CPA follows.

Response to Amendment

2. Acknowledgement is made of applicant having filed an amendment on 01 September 2000 wherein a change was requested at page 30, line 30. The aforementioned amendment has not been entered, as the text does not exist on the identified line. It would appear that line 25, instead of line 30, should be the target of the amendment.

Specification

3. The use of the trademark TRITON X-100 has been noted in this application; see page 30, line 25, and TX100 at page 31. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

6. Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in *In re Wands*, 8 USPQ2d 1400 (CAFC 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The Quantity of Experimentation Necessary

The quantity of experimentation need is great, on the order of several man-years and then with little, if any, reasonable expectation of success.

The Amount of Direction or Guidance Provided and The Presence or Absence of Working

Examples

The amount of direction or guidance provided is limited. Upon review of the specification the following examples have been found:

Example 1, pages 29-34, "Empirically observed Inactive Probes," Table 1, page 33, sets forth 14 probes of which 8 are drawn to human p53 and 6 are drawn to human G3PDH.

Example 2, pages 34-36, "Utilization of Empirically Observed Inactive Probes."

Example 3, pages 36-38, "Probes Forming Highly Stable Intramolecular Structures;"

A. Design of Hairpin Probes as Background Probes

B. Testing of Designed Hairpin Probes as background Probes

Example 4, pages 39-40, "Short Probes."

Example 5, page 41, "Chemically Modified Probes."

Example 6, pages 41-48, "Use of Background Features in Background-Correcting the Signal of the Hybridization Features."

Example 7, pages 48-51, " Use of Background Features in Determinations of LLD."

The Nature of the Invention

The claimed invention relates directly to matters of physiology and chemistry, which are inherently unpredictable and as such, require greater levels of enablement. As noted in *In re Fisher* 166 USPQ 18 (CCPA, 1970):

In cases involving predictable factors, such as that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws. In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved.

The State of the Prior Art

The state of the prior art has advanced to the point where the art of nucleic acid hybridization has recognized certain problems. As set forth in Carrico, (US Patent 5,200,313) the extent and specificity of hybridization is affected by the following principal conditions:

1. The purity of the nucleic acid preparation.
2. Base compositions of the probe - G-C base pairs will exhibit greater thermal stability than A-T or A-U base pairs. Thus, hybridizations involving higher G-C content will be stable at higher temperatures.
3. Length of homologous base sequences- Any short sequence of bases (e.g., less than 6 bases), has a high degree of probability of being present in many nucleic acids. Thus, little or no specificity can be attained in hybridizations involving such short sequences. From a practical standpoint, a homologous probe sequence will often be between 300 and 1000 nucleotides.
4. Ionic strength- The rate of reannealing increases as the ionic strength of the incubation solution increases. Thermal stability of hybrids also increases.
5. Incubation temperature- Optimal reannealing occurs at a temperature about 25 - 30 °C below the melting temperature for a given duplex. Incubation at temperatures significantly below the optimum allows less related base sequences to hybridize.
6. Nucleic acid concentration and incubation time- Normally, to drive the reaction towards hybridization, one of the hybridizable sample nucleic acid or probe nucleic acid will be present in excess, usually 100 fold excess or greater.
7. Denaturing reagents- The presence of hydrogen bond-disrupting agents, such as formaldehyde and urea, increases the stringency of hybridization.

8. Incubation- The longer the incubation time, the more complete will be the hybridization.

9. Volume exclusion agents- The presence of these agents, as exemplified by dextran and dextran sulfate, are thought to increase the effective concentrations of the hybridizing elements thereby increasing the rate of resulting hybridizations.

Further, subjecting the resultant hybridization product to repeated washes or rinses in heated solutions will remove non-hybridized probe. The use of solutions of decreasing ionic strength, and increasing temperature, e.g., 0.1X SSC for 30 minutes at 65 °C, will, with increasing effectiveness, remove non-fully complementary hybridization products.

Further, the claimed invention relates to the use of oligonucleotide arrays. The use of such arrays requires due consideration of the length of the oligonucleotide immobilized thereto as unwanted secondary structures may form between one oligonucleotide and self as well as between any given oligonucleotide and others in the same spot as well as those found in other locations if manufactured in sufficiently close proximity.

The specification of the subject application has been found to be effectively silent as to how these issues are to be resolved in the context of the claimed invention. While attention has been directed to both patent documents and non-patent literature, the specification is essentially silent as to how these prior art methods are to be adapted and modified so as to permit one of skill in the art to practice the full scope of the claimed invention sans resort to undue experimentation. The situation at hand is analogous to that in *Genentech v. Novo Nordisk A/S* 42 USPQ2d 1001. As set forth in the decision of the Court:

“ [T]o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue

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experimentation.' *In re Wright* 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *see also Amgen Inc. v. Chugai Pharms. Co.*, 927 F. 2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed Cir. 1991); *In re Fisher*, 427 F. 2d 833, 166 USPQ 18, 24 (CCPA 1970) ('[T]he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art.').

"Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. *See Brenner v. Manson*, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966) (starting, in context of the utility requirement, that 'a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.') Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention.

"It is true . . . that a specification need not disclose what is well known in the art. *See, e.g., Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific starting material or any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skill in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. This specification provides only a starting point, a direction for further research. (emphasis added)

The Relative Skill of Those in the Art

The relative skill of those in the art that is most closely associated with the claimed invention is high, on par with those that hold a Ph.D. in biochemistry.

The Breadth of Scope of the Claims

The claims are drawn generally to four distinct areas:

- A hybridization assay, claims 10-20, 34-39, and 40-49;
- A method for estimating background noise in a nucleic acid hybridization assay, claims 21-29;
- A kit, claims 34-39; and
- A method of validating a test background feature, claims 30-32.

Claims drawn to the hybridization assay have been interpreted as having sufficient breadth of scope so to encompass the simultaneous detection of any number of nucleic acid sequences that are present simultaneously in a given sample. It is noted that the sample is to comprise "labeled target nucleic acid acids" as well as "a labeled positive control target nucleic acid." There is no requirement that the label on the target and the label on the positive control be different or that the positive control be in any way distinguishable from that of the target nucleic acid. The assay is to also employ "background features" that are to be detectable. Again, there is no requirement that the background feature be labeled any differently or have any property that would distinguish it from that of the labeled target nucleic acid or from the labeled positive control. One is to remove any unbound target nucleic acid. There is no requirement that any unbound positive control be removed or that the background feature be subjected to any washing or dissociation step.

The hybridization assay requires that one subtract the background signal from the observed signal. However, the method seemingly only requires that one "observe" the various signals. Observing a signal, perhaps by eye, and making a quantitative determination are

seemingly different methods yet the claims do not require in all instances that any quantitative means be employed so as to effect a quantitative determination of a target signal, a positive control signal, or of a background signal, be they on the same substrate or on different regions of a common substrate.

As seen in claim 15, the method of claim 10 encompasses the use of a variety of probes.

Included in the listing are:

- empirically observed inactive probes;
- probes forming intramolecular structures
- short probes of 5 to 25 nt in length;
- reverse polarity nucleotide analogs; and
- abasic phosphodiesters or modified nucleotide units.

As shown above, the specification attempts to exemplify some of these probes but not all are. Even where the specification does describe some of the probes, they do not set forth, in sufficient detail, the reaction conditions under which they are to be used such that one of skill in the art would be able to use same without having to resort to undue experimentation. As noted above in *Genentech*, the specification must set forth both the reaction conditions and the starting materials. Such has not happened here.

None of the examples provided are directed to an exemplification of a "method for estimating background noise in a nucleic acid hybridization assay" nor are any of the examples directed to a "method of validating a test background feature." Accordingly, even where the specification has been found to exemplify what is meant by certain probes, the specification has not enabled their use commensurate in scope with the methods.

For the above reasons, and in the absence of convincing evidence to the contrary, claims 10-32 and 34-49 have not been found to be enabled by the subject specification.

Claims 32-39 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. As presently worded, kit claims 34-39 have been interpreted as encompassing any number of probes that can be used to bind to virtually any nucleic acid target. The specification has not been found to provide an adequate written description of the broad genus so as to reasonably suggest that applicant was in possession of same at the time of filing. In support of this position, attention is directed to the decision of *Vas-Cath Inc. v. Mahurkar* 19 USPQ2d 1111 (CAFC, 1991):

This court in *Wilder* (and the CCPA before it) clearly recognized, and we hereby reaffirm, that 35 USC 112, first paragraph, requires a "written description of the invention" which is separate and distinct from the enablement requirement. The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the "applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the "written description" inquiry, whatever is now claimed.

Attention is also directed to the decision in *In re Shokal*, 113 USPQ 283 (CCPA 1957) wherein is stated:

It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. *In re Soll*, 25 C.C.P.A. (Patents) 1309, 97 F.2d 623, 38 USPQ 189; *In re Wahlforss et al.*, 28 C.C.P.A. (Patents) 867, 117 F.2d 270, 48 USPQ 397. The decisions do not however fix any definite number of species which will

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establish completion of a generic invention and it seems evident therefrom that such number will vary, depending on the circumstances of particular cases. Thus, in the case of small genus such as the halogens, consisting of four species, a reduction to practice of three, or perhaps even two, might serve to complete the generic invention, while in the case of a genus comprising hundreds of species, a considerably larger number of reductions to practice would probably be necessary.

We are of the opinion that a genus containing such a large number of species cannot properly be identified by the mere recitation or reduction to practice of four or five of them. As was pointed out by the examiner, four species might be held to support a genus, if such genus is disclosed in clear language; but where those species must be relied on not only to illustrate the genus but to define what it is, the situation is otherwise.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bradley L. Sisson whose telephone number is (703) 308-3978. The examiner can normally be reached on 6:30 a.m. to 5 p.m., Monday through Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Stephanie Zitomer can be reached on (703) 308-3985. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-3592 for regular communications and (703) 308-0294 for After Final communications.

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Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

B. L. Sisson
Bradley L. Sisson
Primary Examiner
Art Unit 1655

BLS
May 18, 2001